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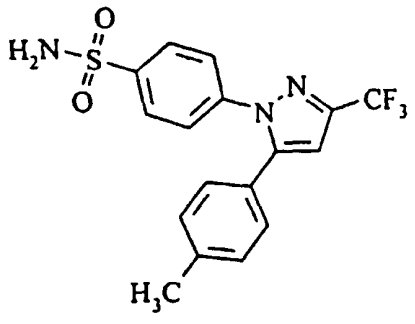
(54) Title: A CRYSTALLINE FORM OF CELECOXIB



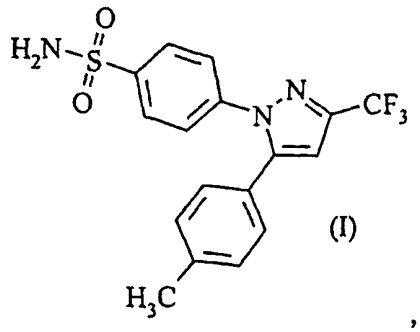
(I)

(57) Abstract: A new crystalline form of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Formula (I), designated as Form I and a method for its production.

WO 02/00627 A1

A CRYSTALLINE FORM OF CELECOXIB

This invention relates to the pharmaceutical therapeutic agent 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide (celecoxib) of formula I



(I)

specifically to a new crystalline form of celecoxib with improved properties. This invention further relates to a method for the production of this crystalline form of the agent.

Since prostaglandins play a major role in the inflammation process, the discovery of non-steroidal anti-inflammatory drugs (NSAIDs) has focused on the inhibition of prostaglandin production, especially PGG_2, PGH_2 and PGC_2 production. The use of NSAIDs in the treatment of pain and swelling associated with the inflammation tends to cause side effects by affecting other prostaglandin regulated processes. Thus NSAIDs tend to cause significant side effects including ulcers.

Previous NSAIDs have been found to inhibit some enzymes including cyclooxygenase. Recently, an inducible form of cyclooxygenase associated with inflammation known as cyclooxygenase II (COX-2) or prostaglandin G/M synthase II has been found to exist. This enzyme is more effective in reducing inflammation, causing fewer and less drastic side effects.

Several compounds selectively inhibiting cyclooxygenase II are described in U.S. Patent Nos. 5 380 738, 5 344 991, 5 393 790, 5 466 823, 5 434 178, 5 474 995, 5 510 368, and International Applications WO 96/06840, 96/03388, 96/03387, 95/15316, 94/15932, 94/27980, 95/00501, 94/13635, 94/20480 and 94/26731.

Certain substituted pyrazolylbenzenesulfonamides, specifically celecoxib (4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide) as selective COX-2 inhibitor and their preparation have been described in International Application WO 95/15316. In addition, an efficient preparation of 3-haloalkyl-1H-pyrazoles in a one-pot synthesis which is suitable for large-scale process has been described in International Application WO 96/37476.

International Application No. WO 00/32189 discloses specific celecoxib compositions. In this document a number of problems concerning the formulation of this agent, inter alia, its cohesiveness, low bulk density, low compressibility, poor solubility, etc., are described. According to this document, these disadvantages are caused by the crystal structure of celecoxib. Unformulated celecoxib, which has a crystal morphology that tends to form long cohesive needles, typically fuses into a monolith mass upon compression in a tablet die, which leads to problems in blending the agent uniformly. Further, low bulk density causes problems in processing the small quantities required in the formulation of pharmaceutical compositions.

It has now surprisingly been discovered that celecoxib may exist at least in two crystalline forms, hereinafter designated as Form I and Form II, having different properties.

Certain organic compounds can exist in several different crystal forms, which can have different chemical and physical properties, such as density, hardness, flow properties, etc. Therefore, new crystal forms of existing compounds are of great interest.

The new crystal form of celecoxib reported herein provides improved properties, making it possible to overcome the problems described in the prior art. Since the new crystal form does not have the disadvantages of the known needle-like crystals, it overcomes the problems disclosed e.g. in WO 00/32189.

The object of the present invention, therefore, is to provide a new crystalline form of celecoxib which avoids the problems produced by the known, needle-like crystalline form.

The solution of this object is provided by the new crystalline form of celecoxib as disclosed herein, which we have called "Form I" of celecoxib, and by the corresponding production method, as also described herein.

Crystalline forms are characterised by means of X-ray powder diffraction patterns. For this purpose a PHILIPS PW 1710 based diffractometer was used and Cu-K_α-radiation (λ (Cu-$K_{\alpha 1}$) = 1.54056 Å; λ (Cu-$K_{\alpha 2}$) = 1.54439 Å) was applied. X-ray diffraction data are provided in terms of 2θ values and corresponding intensities.

The crystalline form of celecoxib designated as Form I according to the present invention is characterised by at least the X-ray powder diffractogram data given in table I:

TABLE I: X-ray Diffraction data of Form I:

Angle [°2θ]	Rel.int [%]
14.800	69.0
16.050	78.9
17.875	63.7
19.615	100.0
21.455	96.6
22.080	68.1
22.385	65.4
23.425	62.5
25.330	64.5
29.355	60.8

In a preferred embodiment of the present invention said crystalline form of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide of Form I is further

characterised by at least the following further X-ray powder diffractogram data given in table II:

TABLE II: Further X-ray Diffraction data of Form I:

Angle [°2θ]	Rel.int [%]
10.670	33.4
10.970	34.0
12.985	32.4
13.855	17.5
18.340	40.4
18.685	40.0
20.425	19.1
20.670	19.0
23.185	48.7
24.510	37.8
24.930	34.5
25.730	22.8
26.915	23.1
27.630	31.5
28.185	26.2
29.955	32.7
30.375	9.9
31.405	9.6
34.915	15.7
35.585	10.9
37.895	17.9
44.070	9.4
45.250	14.5

(in addition to the dominant reflexes of table I).

An example of the X-ray diffraction pattern of Form I is shown in Fig. 1.

The alternative disadvantageous, needle-like crystal form (designated herein as Form II) which is provided by the methods described in the prior art differs significantly from Form I according to the present invention.

An example of the X-ray diffraction pattern for the known Form II is shown in fig. 2 and the corresponding data are given in Table III.

TABLE III: X-ray Diffraction data of Form II

Angle [°2θ]	Rel.int [%]
11.025	27.5
13.285	5.9
15.115	16.5
16.415	91.4
17.625	3.2
18.265	3.6
19.785	5.6
21.820	100.00
22.440	16.9
23.500	2.7
24.620	3.0
25.460	2.7
27.280	21.0
29.885	15.6
31.580	1.5
32.815	9.0
35.185	7.4
38.205	5.8
38.415	4.2
39.695	2.5
40.740	3.7
41.285	0.8
42.960	2.4
43.810	2.7
44.820	4.5
45.415	5.0
46.300	4.9

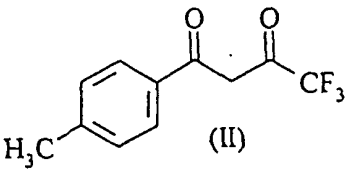
Further, SEM images of the crystallites of Form I according to the invention and Form II obtained by the production methods known in the prior art clearly illustrate the plate like habit of the crystals of Form I in contrast to the needle like habit of the crystals of Form II; as is illustrated by attached Fig. 3 and 4.

One of the main disadvantages of the needle-like crystals of Form II mentioned in WO 00/32189 is their low bulk density. It was found, that the crystals of the invention's Form I are distinctly denser in comparison to the crystals of Form II prepared according to the methods as given in International Applications WO 95/15316 and WO 96/37476. The following densities are typical and characteristic for the crystals of Form I and II, respectively:

	Form I	Form II
bulk density	≥ about 0.270 g/ml	about 0.130 g/ml
tap density	≥ about 0.360 g/ml	about 0.180 g/ml

Consequently, the crystals of Form I are denser than the crystals of Form II, providing improved filtration and drying characteristics. Due to its increased density, better flow properties and lower electrostatic charge, Form I provides further advantages in formulation and capsule preparation.

The present invention further relates to a method for the production of the crystals of Form I of celecoxib by reacting 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione of formula II



(II)

with 4-sulphonamidophenylhydrazine hydrochloride in a suitable solvent, crystallizing the resulting 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide from the reaction mixture and recrystallizing it from a suitable solvent.

1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione may be prepared according to Example 2 Step 1 in International Application WO 95/15316.

The preparation of celecoxib, according to the present invention, differs from the production described in WO 95/15316 mainly by the crystallization system used.

Thus, the dione is preferably reacted with 4-sulphonamidophenylhydrazine hydrochloride in isopropanol, instead of absolute ethanol, at reflux temperature. The reaction mixture is treated with activated carbon; after filtering, the product is preferably obtained by crystallizing it by the addition of a non-solvent, especially water (instead of by concentration of the reaction mixture). Finally, the substance is preferably recrystallized from isopropanol and water, instead of methylenechloride/hexane.

Accordingly, the present invention provides further advantages for the preparation of celecoxib by eliminating methylene chloride, a risk for the environment and human health. In addition, it also eliminates the use of n-hexane which causes an ignition and fire risk due to its electrostatic charge accumulation property. Further, according to the present invention, water replaces n-hexane. The use of isopropanol is a further advantage, since it is commercially available and widely used in chemical industry compared to absolute ethanol. Isopropanol should be anhydrous and may be combined with other hydroxylic solvents. Finally, by precipitating the product from the reaction mixture instead of concentrating the reaction mixture to dryness, a higher purity is achieved.

In order to obtain crystals of Form I, celecoxib is most preferably prepared by dissolving celecoxib in a suitable solvent system comprising at least one amide solvent, preferably selected from the group comprising N,N-dimethylformamide, NN-dimethylacetamide and/or mixtures thereof, N,N-dimethylformamide being most preferred, from which solution the crystals of Form I are obtained by the addition of a non-solvent, especially water.

This recrystallization is generally carried out at temperatures of 0 to 80 °C, particularly of 5 to 70 °C, preferably of 10 to 60 °C, more preferably of 15 to 50 °C, most preferably of 20 to 40 °C, e.g., of 25 to 30 °C and/or ambient temperature.

The present invention further includes crystalline celecoxib of Form I crystallography, obtainable by the above described method of production.

Further, the present invention includes pharmaceutical preparations, comprising crystalline celecoxib according to the present invention. Pharmaceutical preparations according to the present invention may be adapted for oral administration and are conveniently presented in the form of, e.g., tablets, capsules, dragees or the like. The formulations may contain ingredients like pharmaceutically acceptable carriers, excipients, adjuvants, etc. as they are known in the art.

Example

Step a: 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione

4'-Methylacetophenone was dissolved in methanol (25 ml) under nitrogen atmosphere. To the stirred solution was added 25% sodium methoxide in methanol (12 ml). The reaction mixture was stirred for 5 minutes and ethyltrifluoroacetate (5.5ml) was added. After refluxing under nitrogen atmosphere for 24 hours the mixture was cooled to room temperature and concentrated. 10 % hydrochloric acid (100 ml) was added. The mixture was extracted with ethyl acetate (4 x 75 ml). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The product was obtained as an oily residue.

Step b: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide

1-(4-Methylphenyl)-4,4,4-trifluorobutane-1,3-dione (4.14 g) from step a was stirred in isopropanol (75 ml). 4-sulphonamidophenylhydrazine hydrochloride (4.25 g) was added. The reaction mixture was refluxed under nitrogen atmosphere for 24 hours, cooled to room temperature and filtered, The filtrate was treated with activated carbon at 40–45° C. The product was crystallized by adding water (150 ml). The product was recrystallized from isopropanol and water.

Step c: Isolation of Form I

4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (20 g) from step b was dissolved in N,N-dimethylformamide (80 ml) at room temperature. The product was crystallized by addition of water (200 ml). The reaction mixture was stirred for 30 minutes. The product was isolated by filtration, washed with water (3 x 40 ml) and dried. Yield: 18 g.

It corresponded to fig. 3 and showed the X-ray diffraction data presented in fig. 1 and tables I and II.

CLAIMS

1. Crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, characterised by at least the following X-ray powder diffractogram reflexes:

Angle [°2θ]	Rel.int [%]
14.800	69.0
16.050	78.9
17.875	63.7
19.615	100.0
21.455	96.6
22.080	68.1
22.385	65.4
23.425	62.5
25.330	64.5
29.355	60.8

2. The crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide according to claim 1, characterised by at least the following further X-ray powder diffractogram reflexes:

Angle [°2θ]	Rel.int [%]
10.670	33.4
10.970	34.0
12.985	32.4
13.855	17.5
18.340	40.4
18.685	40.0
20.425	19.1
20.670	19.0
23.185	48.7
24.510	37.8
24.930	34.5
25.730	22.8
26.915	23.1
27.630	31.5
28.185	26.2
29.955	32.7
30.375	9.9
31.405	9.6
34.915	15.7
35.585	10.9
37.895	17.9
44.070	9.4
45.250	14.5

3. Crystalline 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, especially according to claim 1 or 2,
characterised in that it has
a tap density of not less than 0.360 g/ml, and/or
a bulk density of not less than 0.270 g/ml.

4. A method for the production of the crystalline substance according to any one of claims 1 to 3,
characterised in that 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione is reacted with 4-sulphonamidophenylhydrazine hydrochloride in a suitable solvent, the resulting 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is crystallized from the reaction mixture and is recrystallized by solvent precipitation from a suitable solvent.

5. The method according to claim 4,
characterised in that the reaction is carried out in isopropanol.

6. The method according to any one of claims 4 or 5,
characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is crystallized from the reaction mixture by the addition of a non-solvent, especially water.

7. The method according to any one of claims 4 to 6,
characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is recrystallized from a solvent system comprising at least one amide solvent.

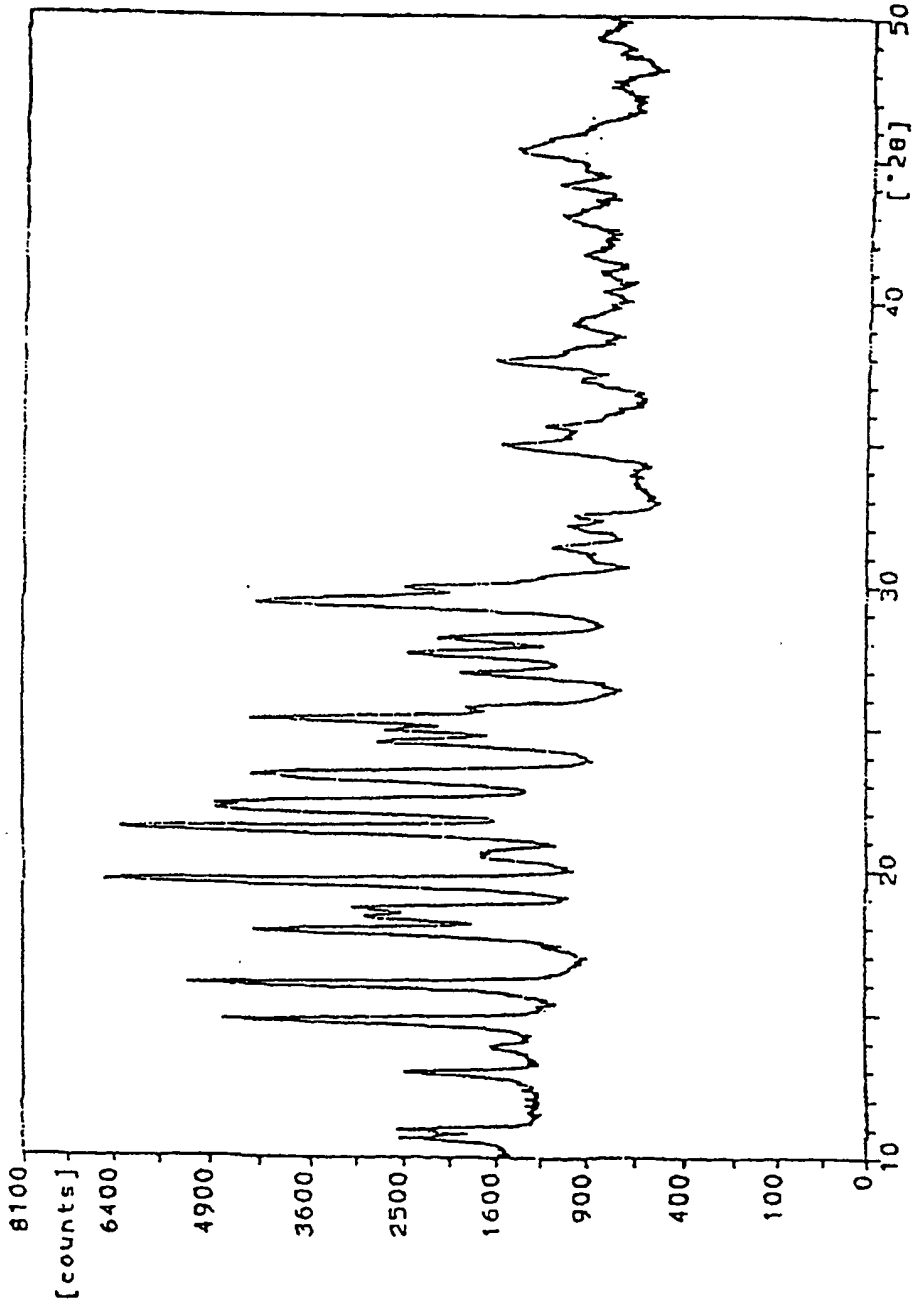
8. The method according to any one of claims 4 to 7,
characterised in that 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide is recrystallized from a solvent system comprising at least one amide solvent by addition of a non-solvent, especially water, at a temperature between 0°C and 80°C.

9. The method according to any one of claims 4 to 8, **characterised in that** the amide solvent is selected from the group, comprising N,N-dimethylformamide, N,N-dimethylacetamide and mixtures thereof.

10. Crystalline 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide in accordance with claims 1,2 or 3, obtainable by the method of any one of claims 4 to 8.

11. A pharmaceutical preparation, comprising crystalline 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide in accordance with any one of claims 1,2,3 or 10.

Figure I


8100
[counts]
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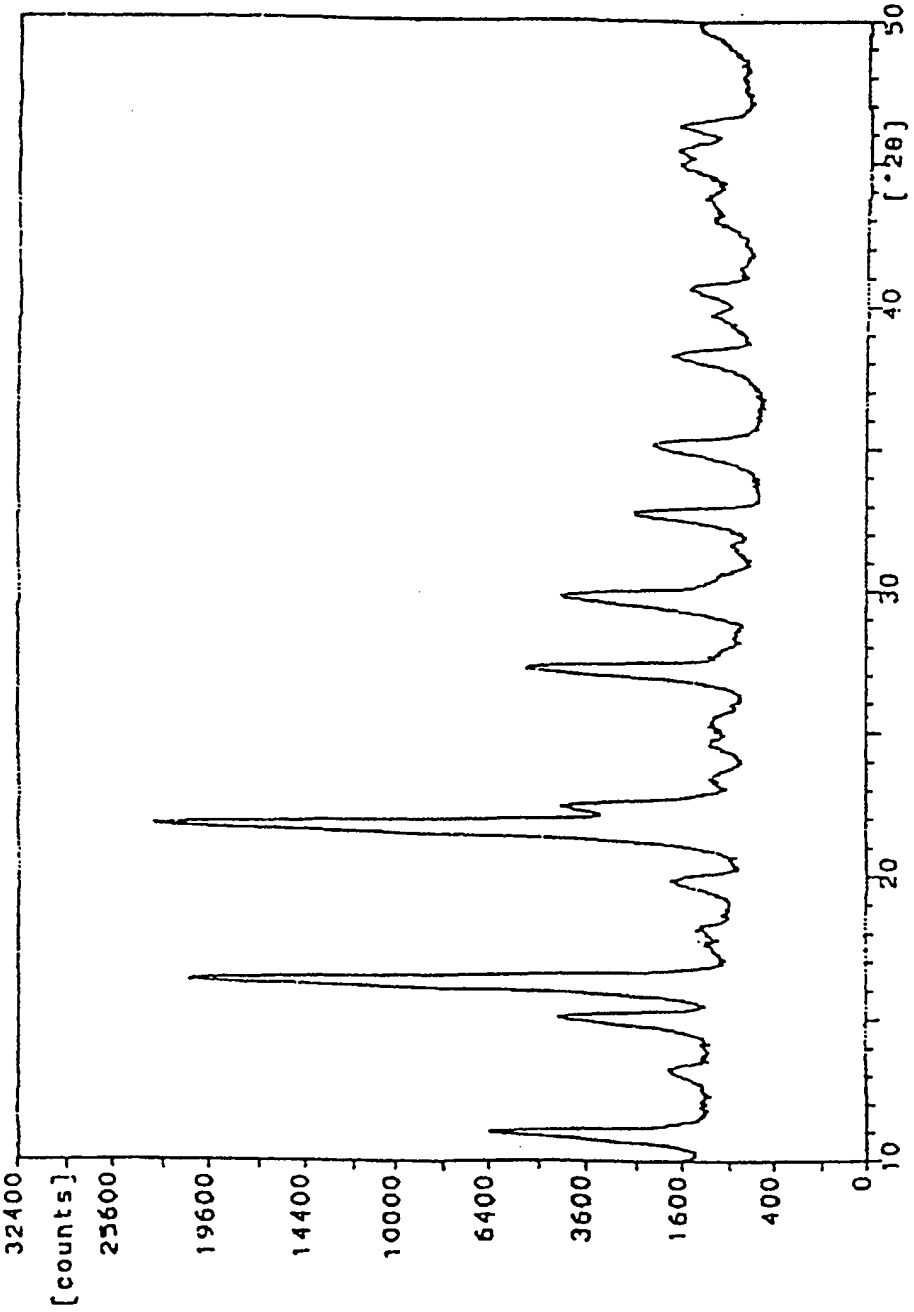
3600
2500
1600
900
400
100
0
10
20
30
40
50
[°2θ]

Figure 2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[counts]
25600
19600
14400
10000
6400
3600
1600
400
0
10
20
30
40
50
[°2θ]

Figure 3: SEM image illustrating the plate like habit of the crystals of Form I:

Figure 3

Figure 4: SEM image illustrating the needle like habit of crystals of Form II:

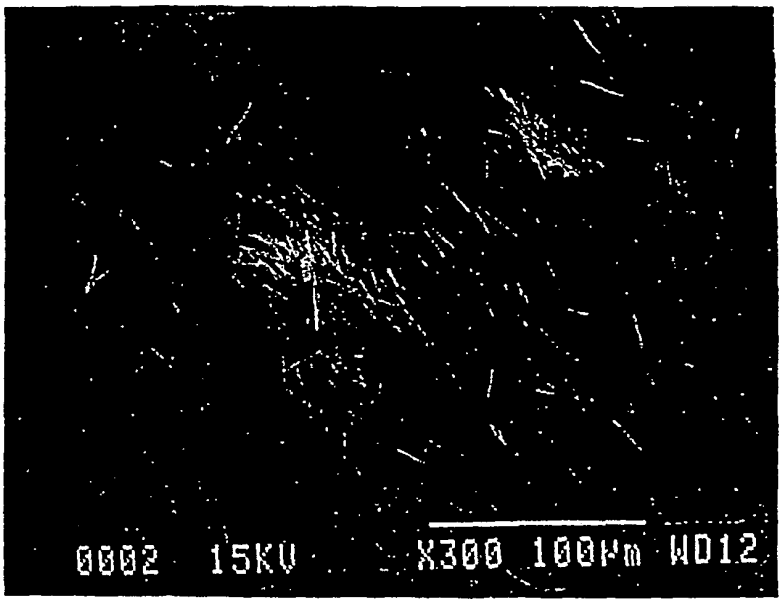
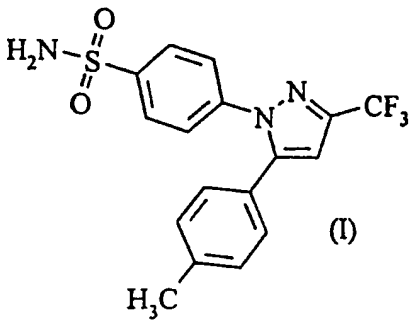


Figure 4

Figure 5



(I)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/TR 01/00025

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D231/12 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 37476 A (SEARLE) 28 November 1996 (1996-11-28) example 1 ---	1-11
X	WO 95 15316 A (GRANETS MATTHEW J ;MIYASHIRO JULIE M (US); SEARLE & CO (US); TALLE) 8 June 1995 (1995-06-08) page 64 -page 65, line 7; example 2 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2001	02/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/TR 01/00025

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	PENNING, THOMAS D. ET AL: "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-'5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1- yl!benzenesulfonamide (SC-58635, Celecoxib)" J. MED. CHEM. (1997), 40(9), 1347-1365 , XP002114833 page 1356, left-hand column, line 18 - line 29 ---	1-3,10, 11
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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